

Sepsis Biomarkers: CRP, Procalcitonin, and Presepsin—Diagnostic and Prognostic Significance in Sepsis

Abstract

Background: Sepsis is undeniably a serious worldwide health threat, causing millions of deaths each year and a real diagnostic challenge to the clinicians. The conventional standard culture methods are often negative and time-consuming; therefore, alternatively specific and easily measurable biomarkers could help in predicting the diagnosis and prognosis of sepsis, as well as monitor the response to the treatments. This study will compare the role of the three markers procalcitonin (PCT), C-reactive protein (CRP), and presepsin in the diagnosis of sepsis in suspected patients admitted to a tertiary care hospital in eastern India. **Materials and Methods:** A hospital-based cross-sectional study was conducted from April 2021 to March 2022. Blood samples were collected from the patients admitted in various intensive care units with evidence of sepsis and the biomarkers were estimated. **Results:** Presepsin was found to be the best among the three biomarkers with sensitivity 89.1% and specificity 88.9%, followed by PCT with sensitivity 82.7% and specificity 80%, and then CRP with sensitivity 74.5% and specificity 75.6%. The diagnostic accuracy of presepsin was also found to be maximum as its area under the receiver-operating characteristic (ROC) curve was highest (0.858) followed by PCT whose area under the ROC curve was 0.793, and then CRP with area under the ROC curve 0.741. **Conclusion:** Based on the result of the present study, biomarkers were found to be quick, easy and effective test for diagnosing sepsis, and presepsin proved to be the most promising marker for diagnosis of sepsis as compared to PCT or CRP.

Keywords: Bacterial sepsis, CRP, presepsin, serum PCT

Introduction

Over centuries, sepsis has remained a real diagnostic challenge to clinicians, causing millions of deaths worldwide each year.^[1] Despite advances in clinical management, sepsis is the leading cause of mortality in critically ill patients.^[2] According to the Third International Consensus, sepsis is defined as ‘a life-threatening organ dysfunction caused by a dysregulated host response to infection,’ devoid of appropriate treatment, sepsis can progress to multiorgan dysfunction and septic shock.^[3] Thus, early recognition of sepsis becomes crucial for better outcomes.^[4]

Blood cultures are a gold standard for diagnosing sepsis. Despite the great advantages, blood cultures also have some limitations: they are often negative, especially in patients previously treated with antibiotics, and their results are usually

obtained over the course of several days.^[5] While waiting for blood culture results, treatment of critically ill septic patients may be delayed, increasing the possibility of poor outcomes.^[6]

Taking the above into consideration, researchers are trying to find an easy measurable and specific sepsis biomarker that will aid in identifying sepsis in patients. Among these biomarkers, some of them are already in use as additional tools incorporated in the list of signs and symptoms introduced in 2001 by The International Sepsis Definitions Conference, such as procalcitonin (PCT) and C-reactive protein (CRP).^[7] Presepsin was first introduced in 2005 as a molecule specifically increased in patients with sepsis compared to healthy controls and patients presenting with non-infectious systemic inflammatory response syndrome.^[8] CD14 is a glycoprotein, a member of the toll-like receptor (TLR) family, constitutively

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Vineeta Baxla,
Ashok Kumar
Sharma,
Kumari Seema,
Abhay Kumar,
Manju Boipai,
Pradip Kumar
Bhattacharya¹,
Manoj Kumar

Department of Microbiology,
Rajendra Institute of Medical
Sciences, Ranchi, ¹Department
of Critical Care Medicine,
Rajendra Institute of Medical
Sciences, Ranchi, Jharkhand,
India

Received: 10-Sep-2024

Accepted: 10-Oct-2024

Published: 04-Feb-2025

Address for correspondence:

Dr. Manoj Kumar,
Department of Microbiology,
Rajendra Institute of Medical
Sciences, Ranchi 834009,
Jharkhand, India.
E-mail: manoj_drmicro@
rediffmail.com

Access this article online

Website:

www.jwacs-jcoac.com

DOI: 10.4103/jwas.jwas_132_24

Quick Response Code:



How to cite this article: Baxla V, Sharma AK, Seema K, Kumar A, Boipai M, Bhattacharya PK, et al. Sepsis biomarkers: CRP, procalcitonin, and presepsin—Diagnostic and prognostic significance in sepsis. J West Afr Coll Surg 2025;15:457-62.



SHOUT **IT**
SHARE

expressed on the cell surface of monocytes/macrophages. The principal ligand of CD14 is bacterial lipopolysaccharide, which when associated with lipoprotein binding protein forms a complex easily recognised by the TLR. CD14 takes two forms: membrane-bound CD14 (mCD14) and soluble CD14 (sCD14). The latter is seen in plasma and is produced by mCD14 fall-off or cell secretion. Presepsin is the 13-kDa N-terminal fragment of soluble CD14 subtype (sCD14-ST).

This study will evaluate the ability of the three biomarkers PCT, CRP, and presepsin to diagnose sepsis and sepsis severity in the patients. It will also compare the markers for clinical informative value and help for early diagnosis of sepsis to enable rapid treatment, improve outcomes, and reduce unnecessary antibiotic therapy.

Materials and Methods

This hospital-based cross-sectional study was conducted from April 2021 to March 2022, and the sample size was 200 for the study. The study was started after getting ethical clearance from Rajendra Institute of Medical Sciences, Jharkhand.

All the patients who were diagnosed with sepsis as suggested by clinical or laboratory features based on the American college of chest and physician guidelines and admitted in the medical intensive care unit (ICU) were included. Patients admitted in the ICU not fulfilling any clinical features of sepsis or SOFA score criteria or with history of malignancy, trauma, recent surgery, burns, or autoimmune disease were excluded from the study.

Blood sample (5mL) was collected from all the patients with evidence of sepsis in the serum separator tube and centrifuged at 3000 rpm for 2 min. Clear serum was used for testing of the biomarkers. As and when the blood samples were obtained, CRP was measured by CRP LATEX KIT (Lab—Care Diagnostics, India). PCT estimation was done by chemiluminescent microparticle immunoassay (ARCHITECT B · R · A · H · M · S PCT). Double antibody sandwich ELISA was done for presepsin using the Human Presepsin (PSPN) ELISA Kit (Shanghai Coon Koon Biotech Co. Ltd).

Statistical analysis

Data were entered, and the template was generated in MS Excel and analysed in Statistical Package for Social Sciences, version 21 (IBM Corp., Armonk, NY, USA). The qualitative data were expressed in the form of frequency and proportion. Necessary pi-diagram and bar charts were drawn. Quantitative data were expressed in mean $\pm$ SD. Appropriate statistical tests were applied according to qualitative and quantitative data.

Results

The final study population consisted of 200 patients. The median age in the study group was 41.5 (95% CI

39.31–44.00, $P < 0.05$) with standard deviation 15.98. The majority of them were males (55%), and 45% were females [Table 1]. According to the SOFA score, the septic patients were classified as follows: 57.5% (septic), 15% (severe sepsis), and 15% (septic shock). Furthermore, the different groups of sepsis were compared based on the demographic data of the patients and associated co-morbidities in each group.

Thus, the most common co-morbidity was diabetes mellitus, followed by hypertension, and then chronic kidney disease, cardiovascular accident and finally bronchial asthma.

A comparison of PCT, CRP, and presepsin among the patients is shown in Figure 1. PCT and presepsin levels were significantly higher in patients with septic shock than in those with sepsis. In contrast, we observed no significant differences in CRP levels between the severe sepsis and sepsis groups.

The validity of the biomarkers was analysed and is shown in Table 2. We found presepsin with the highest sensitivity (89.1%) and specificity (88.9%), followed by PCT with sensitivity (82.7%) and specificity (80%), and finally CRP with sensitivity (74.5%) and specificity (75.6%).

Receiver-operating characteristic (ROC) curve analysis was performed to compare the diagnostic accuracy of the three biomarkers. The ROC curve denotes the diagnostic performance of a test or the accuracy of a test to discriminate between diseased and non-diseased cases. Accuracy is measured by the area under the ROC curve [Figure 2]. An area of 1 represents a perfect test; an area of 0.5 represents a worthless test.

The area under the curve for presepsin was found to be the maximum (0.858), followed by PCT whose area under the ROC curve is (0.793), and then CRP with area under the ROC curve (0.741).

Discussion

Sepsis is one of the important causes of mortality, and its diagnosis and management remains a challenge for

Table 1: Baseline demographic data and associated co-morbid conditions

	sepsis	Severe sepsis	Septic shock	P value
Age (median IQR)	38 (37–42)	47 (43–52)	47 (39–52)	<0.05
Co-morbidity (CVA)	4 (3%)	10 (18%)	2 (6%)	0.24
Hypertension	23 (20%)	7 (13%)	7 (23%)	0.7
CKD	7 (6%)	6 (11%)	9 (30%)	0.163
Bronchial asthma	8 (7%)	1 (2%)	1 (3%)	0.6
Diabetes mellitus	14 (12%)	14 (25%)	10 (33%)	0.68

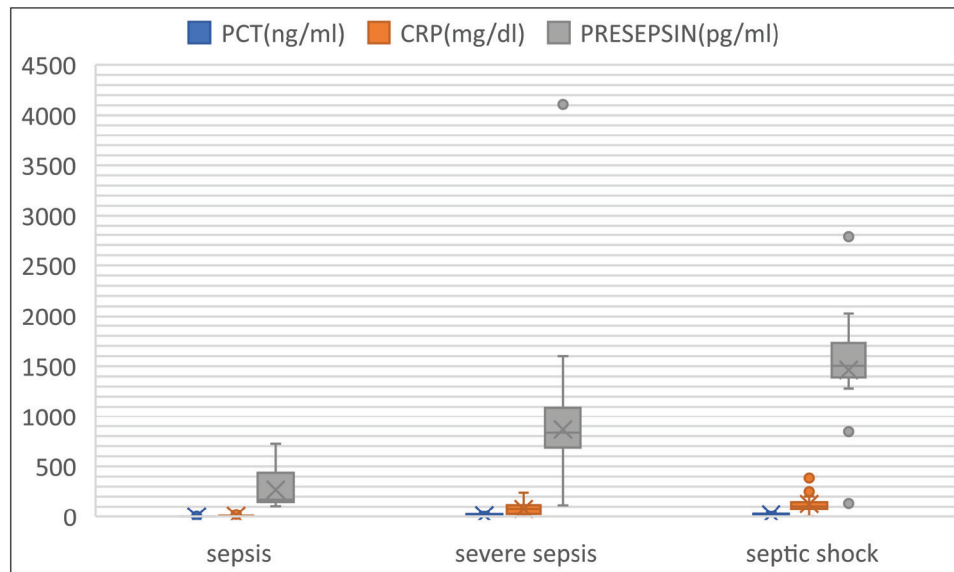


Figure 1: Comparison of procalcitonin, C-reactive protein and presepsin, biomarkers associated with sepsis

Table 2: Statistical analysis of the biomarkers for their sensitivity, specificity, positive predictive value, and negative predictive value

Validity	Procalcitonin	C-Reactive protein	Presepsin
Sensitivity	82.7%	74.5%	89.1%
Specificity	80.0%	75.6%	88.9%
Positive predictive value (PPV)	83.5%	78.8%	90.7%
Negative predictive value (NPV)	79.1%	70.8%	87.9%

healthcare workers. In reducing the mortality rate, early diagnosis of sepsis and instituting antibiotic therapy at the earliest play a crucial role. There is no single reliable test for the early definite diagnosis of sepsis, and therefore, there is a continuing search for a new infection marker. This study demonstrates the potential value of measuring the inflammatory markers presepsin, PCT, and CRP in patients with clinically suspected sepsis and was compared between culture-positive and culture-negative groups.

Blood culture positivity

A positive blood culture is the one of the definitive methods of confirming a case of septicemia, which is a ‘Gold standard’ test and help in prompt and timely administration of antibiotics, which could be lifesaving.

Gram-negative organisms (65%–85%) are found to be frequently responsible for septicemia than Gram-positive organisms (15%), as evidenced by the Indian studies.

In this study, we obtained 110 blood culture-positive (55%) and 90 negative blood culture (45%).

Among the isolated organisms, *Klebsiella* species was found to be 19.1%, followed by *Pseudomonas* species

17.2%, *Escherichia coli* 16.4%, *Acinetobacter* species 16.4%, *Staphylococcus aureus* 7.2%, and *Enterococcus* in 6.4% of cases. Other organisms which were isolated are CONS (5.5%), *Proteus* (8%), and *Candida* (3.6%). The most common organisms grown were *Klebsiella* species, followed by *Pseudomonas*, *Acinetobacter* species, and *E. coli*.

Another study, “Bacteriological profile and Antibiotic sensitivity patterns of blood culture” by Ashwin and Kanth^[9] showed that the most common isolates in the early-onset septicemia were *Klebsiella* species (25.8%), *Enterobacter* species (22.4%), and *E. coli* (14.5%). Isolates in late-onset septicemia *Enterobacter* spp. (23.3%) was the major pathogen, followed by coagulase-negative staphylococcus (23.3%).

Diagnostic value of serum PCT in the study population

In our study, the median value of serum PCT in the group of patients with sepsis was 0.5 ng/mL, in the group of severe sepsis was 7.2 ng/mL, and in the group of patients with septic shock, it was 10.6 ng/mL. Thus, we infer that higher median levels of serum PCT were noticed in the groups with more severe forms of sepsis. Thus, a quantitative correlation of higher values of serum PCT with worse prognosis was established.

In the study by Sudhir *et al.*,^[10] 26.9% of patients belonging to the sepsis group, 36% in the group including severe sepsis cases, and 37.1% of patients in the group consisting of septic shock patients had high serum PCT levels of more than 10 ng/mL. This is similar to the results obtained in our study. This was comparable to various studies done previously by Meisner, Stucker *et al.*^[11,12] in which there was significant statistical association between serum PCT levels and categories of sepsis with $P = 0.001$.

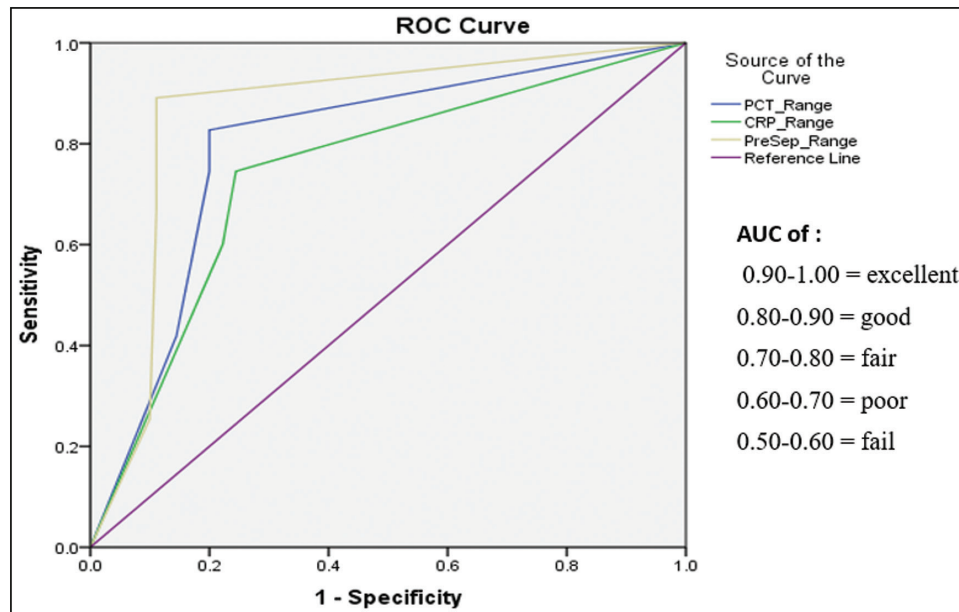


Figure 2: Receiver-operating characteristic curve analysis of biomarkers

PCT co-relation with microbiological yield

In our study, 91 out of 110 patients (82%) who had culture-positive sepsis had positive serum PCT level, whereas 18 of 90 patients (20%) who had culture-negative sepsis had positive serum PCT level. This shows that PCT level rises even in those 18 of the negative culture patients.

Thus, it implies that serum PCT can be used as a complementary diagnostic modality in the diagnosis of sepsis, in addition to its utility in the prognosis of sepsis by quantitative correlation.

Diagnostic accuracy of serum C-reactive protein

CRP production is a non-specific response to disease and cannot be used alone as a diagnostic test for septicemia.

Along with clinical evidence of the disease, CRP provides a good idea regarding septicemia diagnosis.

Tillet and Francis^[13] concluded that it is a protein that helps in complement binding to foreign or damaged cells in response to inflammation and rising to peak levels after 50h.

Effat *et al.*^[14] did a study in a the neonatology unit in KRL general hospital aimed to analyse the role of CRP in neonatal sepsis. It concluded that CRP estimation does have a role in the diagnosis of neonatal sepsis, but the test is not specific enough to be relied upon as the only indicator.

Similarly in our study, regarding CRP positivity, total 104 tested positive and 96 were negative by this marker. My result showed that CRP was positive in 82 out of 110 blood culture positive cases, making the sensitivity of CRP 74.54%. However, it also showed 22 positive values in 90 of the negative culture patients, making the marker comparatively less specific.

Diagnostic accuracy of serum presepsin

This study found 11% positive in the sepsis range, 23.5% in the severe sepsis group, and 18.5% in the septic shock group according to presepsin values in the serum of the study group.

Presepsin showed the best result as it detected maximum 98 positive out of 110 culture positive cases, making the sensitivity of the marker 89.09%. Although they were also positive in 90 of the total culture-negative cases, but this true-positive result in case of presepsin was minimum. Thus, we can say presepsin was highly specific among the other markers as the specificity was 88.88%.

This was seen also in Ulla *et al.*^[15] study who found a significant correlation between presepsin levels and SOFA score on admission, as a severity index of organ failure. Moreover, the level of presepsin was seen in data from the ALBIOS study to be correlated with SOFA score and hemodynamic stability. There was a strong significant positive correlation between presepsin levels and severity of sepsis in our study, which was also shown by Shozushima *et al.*^[16] Kojika *et al.*^[17] which showed a significant correlation between presepsin values and both APACHE II and SOFA scores.

These findings strengthened the hypothesis of presepsin use for prediction of more severe infection and reflecting patient condition.

Comparison of the three markers C-reactive protein, procalcitonin, and presepsin

When comparing the three markers, we found presepsin with maximum sensitivity (89.1%) and specificity (88.9%), followed by PCT with sensitivity (82.7%) and specificity (80%), and then CRP with sensitivity (74.5%) and specificity (75.6%).

When they were compared in the ROC curve, the highest area under the curve was of presepsin 0.858, and then we had PCT with area 0.793, and lastly CRP with area 0.741.

A similar result was found in Brenner *et al.*^[18] study which showed presepsin with sensitivity (91%), specificity (67%), and AUC 0.83; PCT showed sensitivity (77%), specificity (78%), and AUC 0.84; and CRP with sensitivity (67%), specificity (85%), and AUC 0.79.

Another study Takahashi *et al.*^[19] had a similar result, presepsin having sensitivity (80%), specificity (83%), and AUC 0.89; PCT showed sensitivity (77%), specificity (76%), and AUC 0.85; and CRP with sensitivity (72%), specificity (95%), and AUC 0.82.

Outcome in the study population

In our study, 164 patients survived at the end of the study period, and 36 patients did not survive, with the mortality rate of 18%. Of the 115 patients in the sepsis group, four patients did not survive, with the mortality rate of 3.47%. Of the 55 patients in the severe sepsis group, 14 did not survive, with the mortality rate being 25%. Of the 30 patients in the septic shock group, 18 did not survive, with the mortality rate of 60%. Thus, with the increasing severity of sepsis, the mortality rate increased. There was significant association between severity of outcome and study population with the *P* value being 0.001 in this study.

In the study by Sudhir *et al.*,^[10] mortality was seen in 23 patients (23%). A study by Kojika *et al.*^[17] showed that mortality in patients with sepsis from various centres varied between 16.8 and 31.8%. Sands *et al.*^[20] who studied sepsis in eight academic medical centres reported a mortality rate of 34%.

Conclusion

Based on the results of this study, presepsin is a superior marker for diagnosis of sepsis as compared to PCT. This study showed the sensitivity of presepsin more than PCT. Even the AUC for presepsin was more than that of both PCT and CRP, which makes the diagnostic accuracy of presepsin the best among PCT and CRP.

The diagnostic accuracy of PCT was more when compared to that of CRP in my study as shown by the AUC in the receiver operating characteristic curve. We also found that PCT was highly sensitive and specific in differentiating the bacterial cause of septic fever from other causes. However, CRP is an early indicator if the patient is resolving so could be utilised as a guide to the clinician to modify the treatment if required.

Ethical approval

The study protocol was approved with Ethics Committee with Ethical Approval No: IEC 175/ Dated March 27, 2021.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.
2. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med* 2013;369:840-51.
3. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Harrison's Manual of Medicine. 20th ed. New York: McGraw-Hill Education; 2020.
4. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, *et al.* Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013;41:580-637.
5. Zadroga R, Williams DN, Gottschall R, Hanson K, Nordberg V, Deike M, *et al.* Comparison of 2 blood culture media shows significant differences in bacterial recovery for patients on antimicrobial therapy. *Clin Infect Dis* 2013;56:790-7.
6. Ferrer R, Artigas A, Suarez D, Palencia E, Levy MM, Arenzana A, *et al.*; Edusepsis Study Group. Effectiveness of treatments for severe sepsis: A prospective, multicenter, observational study. *Am J Respir Crit Care Med* 2009;180:861-6.
7. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, *et al.*; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. *Crit Care Med* 2003;31:1250-6.
8. Yaegashi Y, Shirakawa K, Sato N, Suzuki Y, Kojika M, Imai S, *et al.* Evaluation of a newly identified soluble CD14 subtype as a marker for sepsis. *J Infect Chemother* 2005;11:234-8.
9. Ashwin RK, Kanth SU. Bacteriological profile and antibiotic sensitivity patterns of blood cultures. *Int J Contemp Pediatr* 2016;3:1221-6.
10. Sudhir U, Venkatachalaiah R, Anilkumar T, Rao MY, Kempegowda P. Significance of serum procalcitonin in sepsis. *Indian Crit Care Med* 2011;15:15.
11. Stucker F, Herrmann F, Graf JD, Michel J-P, Krause KH, Gavazzi G. Procalcitonin and infection in elderly patients. *J Am Geriatr Soc* 2005;53:1392-5.
12. Meisner M. Procalcitonin (PCT) – A New, Innovative Infection Parameter. *Biochemical and Clinical Aspects*. New York: Thieme Stuttgart; 2000.
13. Tillet WS, Francis T, Jr. Serological reactions in pneumonia with a nonprotein fraction from pneumococcus. *J Exp Med* 1930;52:561-71.
14. Effat H, Aliya H, Sughra W, Ghulam R. Validity of C- reactive protein (CRP) for diagnosis of neonatal sepsis. *Pak J Med Sci* 2015;31:527-31.
15. Ulla M, Pizzolato E, Lucchiari M, Loiacono M, Soardo F, Forno D, *et al.* Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: A multicenter prospective study. *Crit Care* 2013;17:R168.
16. Shozushima T, Takahashi G, Matsumoto N, Kojika M, Okamura Y, Endo S. Usefulness of presepsin (sCD14-ST) measurements as a marker for the diagnosis and severity of sepsis that satisfied

- diagnostic criteria of systemic inflammatory response syndrome. *J Infect Chemother* 2011;17:764-9.
17. Kojika M, Takahashi G, Matsumoto N, Kikkawa T, Hoshikawa K, Shioya N, *et al.* Serum levels of soluble CD14 subtype reflect the APACHE II and SOFA scores. *Med Postgraduates* 2010;48:46-50.
 18. Brenner T, Fleming T, Uhle F, Silaf S, Schmitt F, Salgado E, *et al.* Methylglyoxal as a new biomarker in patients with septic shock: An observational clinical study. *Crit Care* 2014;18:683.
 19. Takahashi G, Shibata S, Ishikura H, Miura M, Fukui Y, Inoue Y, *et al.* Presepsin in the prognosis of infectious diseases and diagnosis of infectious disseminated intravascular coagulation: A prospective, multicentre, observational study. *Eur J Anaesthesiol* 2015;32:199-206.
 20. Sands KE, Bates DW, Lanken PN, Graman PS, Hibberd PL, Kahn KL, *et al.* Academic Medical Center Consortium Sepsis Project Working Group. Epidemiology of sepsis syndrome in 8 academic medical centers. *JAMA* 1997;278:234-40.